Pharmacokinetics and pharmacodynamics of the novel somatostatin-dopamine chimeric compound BIM23B065 and its metabolite during a growth hormone stimulation test

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INTRODUCTION

- BIM23B065 is a novel somatostatin-dopamine chimeric compound designed to reduce excessive growth hormone (GH) secretion in patients with acromegaly.
- First-In-Human study to investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of BIM23B065.
- Phase I, double-blind, randomized, placebo-controlled study.

OBJECTIVES

- To quantify the pharmacokinetics of BIM23B065 and its main metabolite (BIM23B133)
- To characterize the response to a GH stimulation test after treatment with BIM23B065
- To identify covariates that influence the PK and PD of BIM23B065

METHODS

- The study consisted of two parts:
  1) SAD: 0.1 mg, 0.4 mg, 0.8 mg, 1.2 mg, and 1.5 mg
  2) MAD: 1.2 mg q.d., 0.8 mg b.i.d., and 1.0 mg b.i.d.
- 6 active and 2 placebo treated subjects per cohort.
- The duration of the MAD was 13 days, including a 6 day up-titration period.
- GH stimulation tests were performed on 2 occasions (day 7 and day 13) in the MAD study.
- 1 µg/kg growth hormone releasing hormone (GHRH) was administered 1 hour after dosing of BIM23B065/placebo to stimulate GH release.
- Population PK/PD modeling was conducted using NONMEM:
  - 1/2/3 compartment models with linear or non-linear absorption and elimination kinetics were explored.
  - A total of 453 BIM23B065, 589 metabolite, and 276 plasma GH concentrations were used for model building.

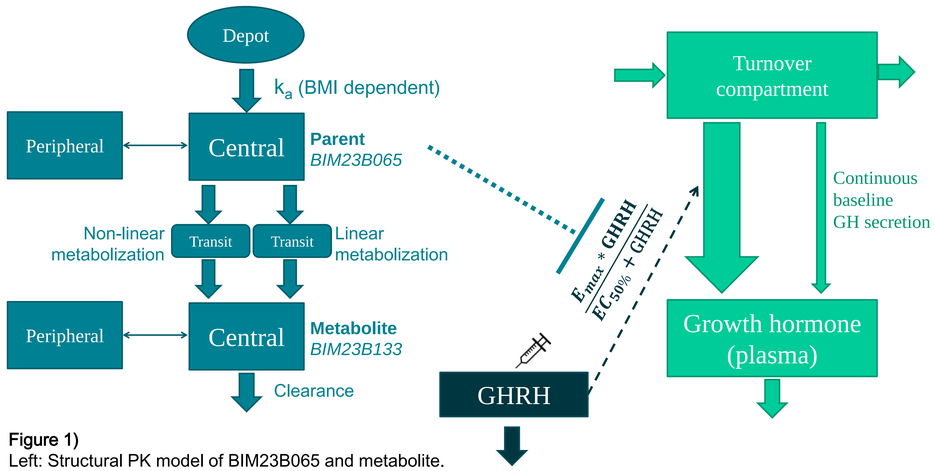

Figure 1)
Left: Structural PK model of BIM23B065 and metabolite.
Middle: Structural PK model of growth hormone releasing hormone.
Right: Structural PD model for GH release in a GH stimulation test.

Table 1) Pharmacokinetic model parameter estimates for BIM23B065 and its main metabolite (BIM23B133) and relative standard errors (RSE%).

Parameter	Estimate [RSE%]
$k_{a\text{-intercept}}$ (/h)	2.41 [14]
$k_{a\text{-slope}}$ (/h/23.31kg/m^2)	-1.35 [22.4]
$V_{central\text{-}parent}$ (L)	8.76 [40.7]
$V_{peripheral\text{-}parent}$ (L)	334 [22]
Q_{parent} (L/h)	41.5 [11.1]
Linear metabolization parent (L/h)	21.8 [45.9]
$V_{max\text{-}parent}$ (mg/h)	0.0788 [22]
KM_{parent} (µg/L)	0.673 [28.7]
Transit $rate_{non\text{-}linear}$(/h)	0.332 [13.3]
Transit $rate_{linear}$(/h)	0.22 [6.26]
$V_{central\text{-}metabolite}$ (L)	5.51 [13.7]
$V_{peripheral\text{-}metabolite}$ (L)	4230 [1.58]
$Q_{metabolite}$ (L/h)	11.1 [7.61]
$CL_{SAD\text{-}metabolite}$ (L/h)	10.5 [7.35]
$CL_{MAD\text{-}metabolite}$ (L/h)	18.5 [8.1]
$k_{el\text{-}GHRH}$* (/h)	4.16

** Indicate fixed parameters*

Table 2) Pharmacodynamic model parameter estimates and relative standard errors (RSE%).

Parameter	Estimate [RSE%]
k_{in} (mU/L/h)	43.3 [26.5]
k_{out} (/h)*	0.279
Baseline secretion (mU/L/h)	0.916 [23.5]
$E_{MAX\text{-}GHRH}$ (/h)*	1
$EC_{50\%\text{-}GHRH}$ (µg)	0.055 [52.3]
Proportional effect BIM23B065 on $EC_{50\%}$	3000 [38.5]
$k_{el\text{-}GH}$ (/h)*	2.2

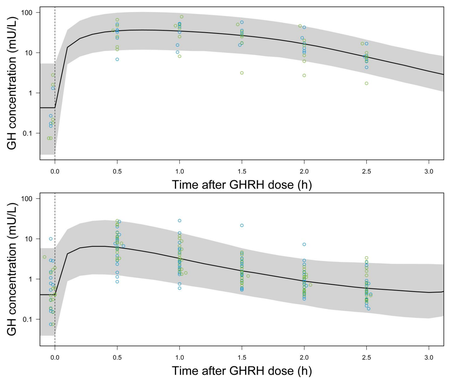

Figure 2) Median growth hormone concentration (black solid line) and 95%-prediction interval (grey area) of placebo (top) and BIM23B065 treated individuals (bottom). Open dots show GH observations from occasion 1 at day 7 (blue) and occasion 2 at day 13 (green). Vertical dotted grey line is time of GHRH administration.

RESULTS

- The PK of BIM23B065 and its metabolite were best described using 2-compartment models.
- BMI negatively influenced the absorption rate constant of the subcutaneous administration of BIM23B065.
- GHRH stimulates GH release following an E_{max} relationship.
- Treatment with BIM23B065 gave a 3000 times increase in the $EC_{50\%}$ of the GHRH effect, thereby reducing the GH release after administration of GHRH.
- The inhibition of the GH release was similar after 7 and 13 days of treatment

CONCLUSIONS

- The PK of BIM23B065 and its metabolite as well as GH release were well described by the model.
- GH release was significantly reduced in BIM23B065 treated subjects after a GH stimulation test.

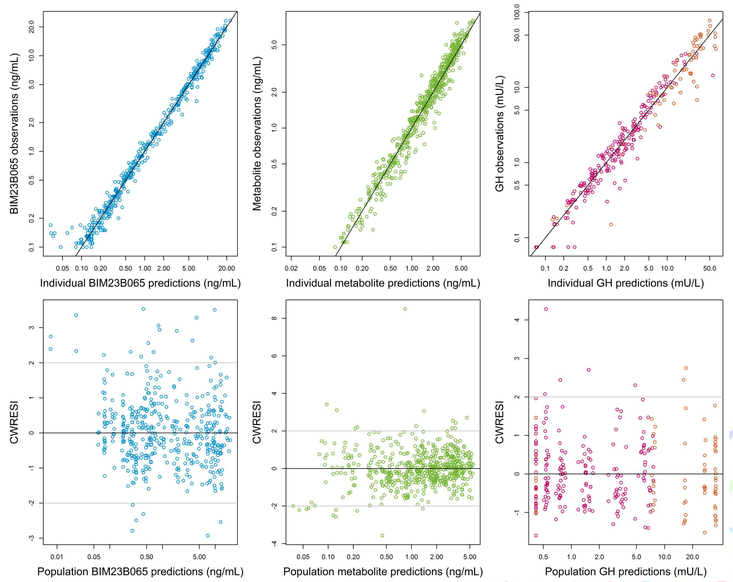

Figure 3) Top: Individual model predictions versus observations for BIM23B065, metabolite and GH concentrations (orange = placebo, fuchsia = BIM23B065 treated).
Bottom: Population model predictions versus conditional weighted residuals with interaction for BIM23B065, metabolite and GH concentrations (orange = placebo, fuchsia = BIM23B065 treated).

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